A4 concl'd. SUBC3 cont

16. (New) The method of claim 15 further including the step of administering an effective amount of a synthetic nuclease resistant antisense oligodeoxynucleotide which targets exon sequences flanking donor splice sites.

REMARKS

Claims 3-12 are currently pending in the application. Only claims 3, 5 and 9 are in independent form.

Claims 5 and 7 stand rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Office Action states that claim 5 recites the phrase "a synthetic nuclease resistant antisense oligodeoxynucleotide capable of selectively modulating". The term "capable" as recited in this claim is considered vague and indefinite. Accordingly, the term "capable" has been removed and instead this claim recited "a synthetic nuclease resistant antisense oligodeoxynucleotide for selectively modulating".

The Office Action also holds that claim 7 recites the term "tunor" and it is believed that this term is spelled improperly and should recite "tumor". Accordingly, this typographical error has been fixed to recite "tumor".

Claims 3-4 and 7-10 stand rejected under 35 U.S.C. Section 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action states that claims 3-4 and 7-10 are drawn to pharmaceutical compositions comprising a synthetic nuclease resistant antisense oligodeoxynucleotide, compositions comprising antisense oligodeoxynucleotides which selectively modulate human tumor necrosis factor alpha, and methods of modulating the expression of human tumor necrosis factor in a mammal. Further, it is stated that there are no general guidelines for the successful *in vivo* delivery of antisense/ribozyme compounds currently not in the art, nor are such guidelines provided in the specification as filed. *Crooke (1998)*, is cited for the conclusion that "extrapolations from in vitro uptake studies to predictions about in vivo pharmacokinetic behavior are entirely inappropriate". Therefore, the Office Action states that the specification does not describe the pharmaceutical compositions comprising antisense oligodeoxynucleotides targeting human tumor necrosis factor alpha, and methods of use of said compositions recited in these claims in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation.

However, the method as cited in the present claims was tested *in vivo* in mice as presented in the attached article by Neuraths et al. This paper details using effective amounts of at least one active ingredient which is a synthetic nuclease resistant antisense oligodeoxynucleotide for regulating mammalian tumor necrosis factor alpha in a mammal. Accordingly, since the Neuraths et al. article utilizes the method set forth in the present application, there is sufficient detail present in the present application so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. Additionally, as shown by the attached articles by Neuraths et al., Bennett et al., Nyce et al., and Wojcik et al., there is increasing evidence showing that in vivo results can be shown based on the in vitro laboratory studies. These are all articles published prior to the priority date of the present application showing that it was known by those skilled in the art that the *in vitro* results of the present invention could be utilized to show the expected *in vivo*

results of such experimentation. Hence, undue experimentation is not required and the claims are enabled.

Claim 7 stands rejected under 35 U.S.C. Section 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey one skilled in the relevant art the inventors, at the time the invention was filed, had possession of the claimed invention.

Specifically, the Office Action states that claim 7 reads on compositions comprising antisense oligodeoxynucleotides capable of selectively "modulating" mammalian tumor necrosis factor alpha. However, claim 7 has been amended to state "regulating" mammalian tumor necrosis factor alpha.

Claim 7, according to the Office Action, also recited a pharmaceutical composition for selectively modulating mammalian "tumor" necrosis factor alpha in a mammal. The specification as filed describes only a single class of mammalian tumor necrosis factor alpha, human tumor necrosis factor alpha. The Office Action states that the specification as filed does not provide any guidance or information of other mammalian tumor necrosis factor alpha mRNAs or proteins of other mammals that would one to predict the structure of these target molecules or potential target sites that would be susceptible to antisense inhibition. Therefore, the Office Action concludes that Applicants are not in possession of antisense oligodeoxynucleotides which modulate a human necrosis factor alpha gene from any other source than human. However, the application does provide a detailed analysis of the effect of the synthetic antisense oligodeoxynucleotides in murine cells. This is

established in the examples, specifically at pages 29-39 wherein the examples detail the effect of the AS-ODN treatment on murine macrophages. Accordingly, there is sufficient detail in the application to show that Applicants were in possession of antisense oligodeoxynucleotides which modulate a mammalian tumor necrosis factor alpha gene from sources other than humans at the time the application was filed.

Claims 5-12 stand rejected under 35 U.S.C. Section 112, first paragraph, because the specification, while being enabling for inhibition of an expression of human tumor necrosis factor alpha in vitro, does not reasonably provide enablement for inhibition of expression of human tumor necrosis factor alpha in vivo, nor does it provide enablement for "modulation" of expression of human tumor necrosis factor alpha, in vitro or in vivo. The Office Action states that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to practice the invention commensurate with the scope of the claims.

Specifically, the Office Action states that the claims are drawn to compositions comprising antisense oligodeoxynucleotides "capable of selectively modulating" human tumor necrosis factor alpha and methods of administering said compositions. If the scope of the claims are truly limited to antisense-based nucleic acid molecules, only inhibition is enabled, not modulation, since modulation implies both increasing and decreasing the expression or activity of a molecule. Therefore, since the specification does not teach an increase in expression and/or stability and since the state-of-the-art of antisense/ribozime teaches only inhibition, Applicants claim to "modulate" is not enabled to the extent that it reads on an antisense/ribozime based system.

However, as stated previously, the claims have been amended to state "regulation" which is defined on page 7 of the application lines 20-22 stating that regulation "it is meant that the expression of the TNF-ALPHA is inhibited or reduced by the action of the AS-ODNs thus indicating that only inhibition of the expression is claimed. Additionally, as stated previously, there is support for the use of the present method in vivo since there is knowledge in the art at the time the application was filed for the use of taking in vitro results and showing their use in vivo and showing the results which can be obtained in vivo. Further, as shown previously, the method of the present application has been conducted in vivo and has achieved the desired results as claimed in the presently pending independent claims. Accordingly, there is sufficient enablement in the specification for in vivo results and enablement for the term "regulation".

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES

Kenneth I. Kohn
Registration No. 30,955
30500 Northwestern Highway
Suite 410
Farmington Hills, MI 48334
(248) 539-5050

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Express Mail Mailing Label No.: EL 358 311 628 US
Date of Deposit: November 15, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, DC 20231 BOX CONTINUATION APPLICATION.

Constance McLean